Background: As a mostly used epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), gefitinib significantly prolongs survival of lung adenocarcinoma patients with EGFR mutations. However, more than 10% of EGFR mutation-positive patients do not respond and a substantial fraction of responded patients progress after 8-12 months’ treatment. Identification of new biomarkers for EGFR-TKIs prognosis is vital. The objective of this study is to explore associations between MDM4 genetic variant and survival of lung adenocarcinoma patients treated with gefitinib.

Methods: 384 patients with stage IIIB or IV lung adenocarcinoma were recruited between January 2009 and June 2013. Patients were treated with gefitinib orally at a daily dose of 250 mg as 1st-line monotherapy. MDM4 rs4245739 A>C genotypes were determined using MassArray system. Dual luciferase reporter gene assays evaluated the function of MDM4 rs4245739 genetic variant in lung adenocarcinoma cell lines A549 and H1299. The differences of patient clinical characteristics were calculated by student’s t test or χ² test. Survival differences were examined by log-rank test. Multivariate Cox regression analysis assessed prognostic factors for PFS or OS. Two-sided P < 0.05 indicated a significant difference.

Results: Among 384 patients, EGFR mutations were positive in 181 patients (47.1%). Median progression-free survival (PFS) and overall survival (OS) for all patients with the rs4245739AC genotype were significantly longer than that of the AA carriers (PFS: 22.9vs.10.9 months, P < 0.001; OS: 27.3vs.16.5 months, P = 0.003). Notably, in the EGFR mutant subgroup, individuals with MDM4 rs4245739AC genotype showed 14.1 months prolonged PFS (28.8 months vs. 14.7 months; P = 0.022) and 12.2 months prolonged OS (31.4 months vs. 19.2 months; P = 0.047) compared to the AA group. Reporter gene assays showed that the rs4245739A allele leads to significantly increased MDM4 expression in lung adenocarcinoma cells compared to the C allele (P < 0.05).

Conclusions: MDM4 rs4245739 genotypes may act as prognostic biomarker for patients’ survival to gefitinib therapy and offer help to individualized treatment in lung adenocarcinoma patients with EGFR mutations.

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